Stakeholder Perspective: SNM

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^{18}F-FDG - Molecular Imaging as Anatomical Contrast Imaging?

FDG to Predict Response to Gleevec

21 patients with GIST and other STS imaged pre and

8 days post chemo:

EORTC criteria for response

PET response seen in 13/21

(*CT response in 10/21 at 8 weeks*)

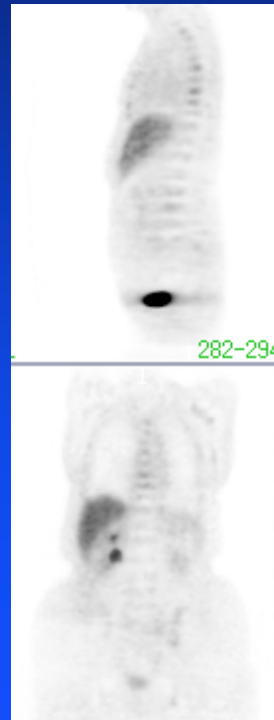One year PFS in responders -   92%

One year PFS in non-responders - 12%

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Stroobants, et al. *Eur J Cancer* 2003; 39: 2012 - 2020

Molecular Imaging and Personalized Medicine

FDG
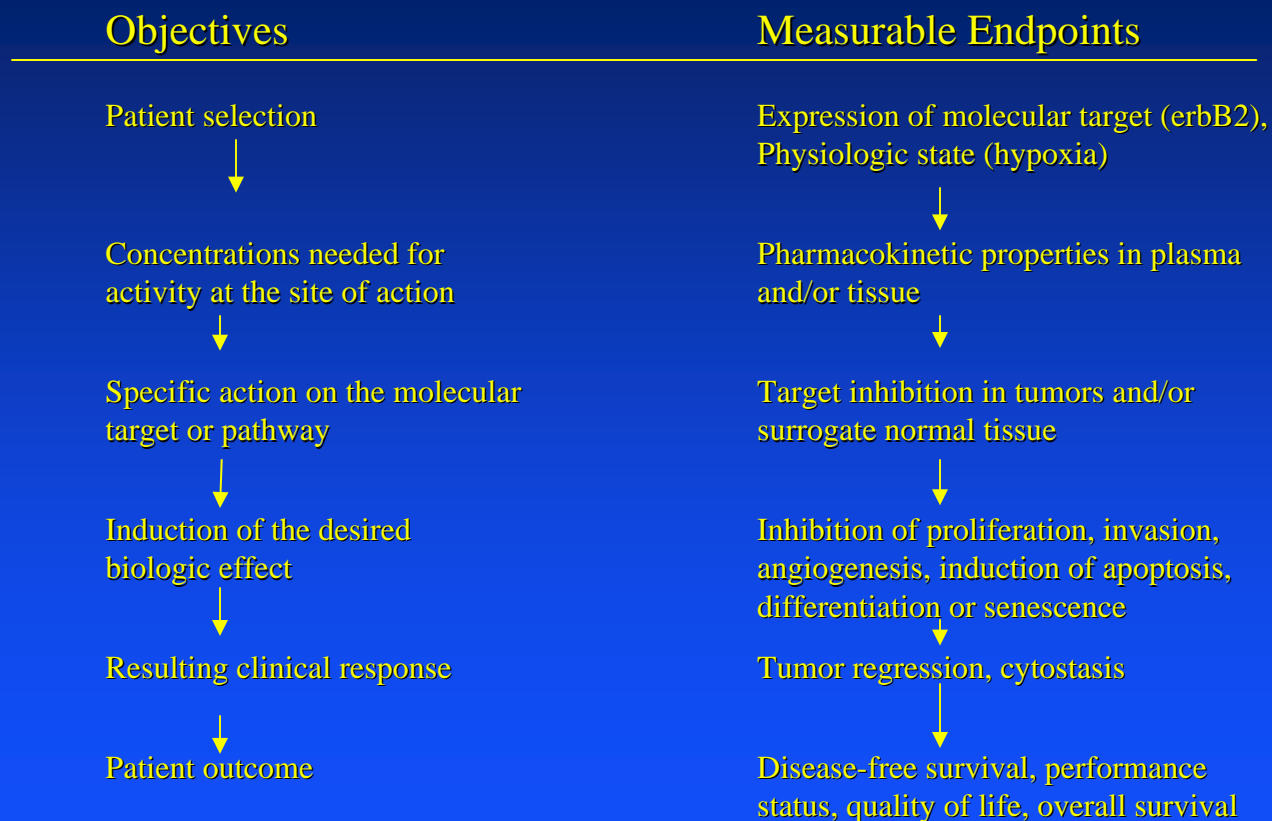
FES

Molecular Imaging

- Predictive assay of treatment response
- Phenotypic characterization
- Treatment selection
- Treatment stratification
- Treatment planning
- Individualized (personalized) medicine
- Improved patient outcomes
- FLT, FES, FAZA, PIB, MET………..
- Requires quantitative understanding of tracer distribution and uptake

Molecular Imaging: Radiotracers in Clinical and Translational Research

- To understand normal functioning of molecules, cells, organs and organisms.

- To assess the biological nature of disease early and throughout its evolution

- To assess progressive developmental, degenerative and disease changes in vivo.

- To facilitate drug discovery and development

- To provide biological information for the development and assessment of innovative therapies.

- To predict, monitor and measure treatment response

- Clinical practice

What is Measurable with Molecular Imaging

Objectives	Measurable Endpoints
Patient selection	Expression of molecular target (erbB2), Physiologic state (hypoxia)
↓	↓
Concentrations needed for activity at the site of action	Pharmacokinetic properties in plasma and/or tissue
↓	↓
Specific action on the molecular target or pathway	Target inhibition in tumors and/or surrogate normal tissue
↓	↓
Induction of the desired biologic effect	Inhibition of proliferation, invasion, angiogenesis, induction of apoptosis, differentiation or senescence
↓	
Resulting clinical response	Tumor regression, cytostasis
↓	↓
Patient outcome	Disease-free survival, performance status, quality of life, overall survival

From Fig 1: Minimally Invasive Pharmacokinetic and Pharmacodynamic Technologies in Hypothesis-Testing Clinical Trials of Innovative Therapies.

Issues Associated with Dissemination of PET Radiotracers/MI into Clinical Practice

- Development of PET tracers
  - Regulations
  - GCP/GMP
- Clinical trials
  - Design, conduct, validation, quantification
  - Definition of response/Outcomes/Imaging biomarkers
  - Outcomes research/Genomic profiling/Treatment planning
- Data confidence
  - Clinical practice issues
  - Health Technology Assessment

SNM Clinical Trials Group:
Address Issues Associated with MI Radiotracers

- Development of PET tracers
  - GMP/GCP
- Validation and standardization of quantitative tracer uptake
- Clinical trials
  - Design and conduct
  - Definition of response/Outcomes/Imaging biomarkers
  - Outcomes research/Genomic profiling/Treatment planning
- Integration with other imaging methodologies
- Clinical practice issues
- Health Technology Assessment

Standardization Requirements

- Quantification of radiotracer uptake/PK/PD
  - Must be robust and translatable across platforms and sites
  - Kinetic modelling
  - Absolute - µgm/gm/min
  - Quantitative - T/B, T/M, T/NT
  - Semi-quantitative - SUV
  - Relative
- Validation and standardization of quantification
  - Across platforms
  - Between sites
  - Radiotracer specificity
- Define correlative outcomes required for imaging biomarkers

Three Models for Standardization and Validation of Radiotracer Quantification

- Preclincal phantom studies

- Preclinical-clinical validation

- Clinical outcomes measures

Stage 1: What is Our Current Capability in Measuring Radiotracer Uptake

- 9 - 12 center study representing all major manufacturers
  - 3 measurement time points
- Two phantoms shipped to each center
  - Long lived Germanium-68 phantom
  - Fillable Fluorine-18 phantom
- Background and tumor sphere activity
- Data analysis - SUV, T/NT ratios
  - Manufacturers software
  - Independent software platform
  - Innovative quantitative approaches

Funded by SNM and CORAR

Stage 1 Outcomes

- Cross platform comparison and validation

- Comparison and validation between centers

- Inter-center temporal comparison and validation

- SUV -v- non-SUV based quantification

- Sources of error

- Recommendations for correcting variables

Stage 2a: Correlating Phantom Data with ^{18}F-FDG Uptake in Patients

- Multi-center study representing all major manufacturers
- Same phantoms as stage 1
- Compare phantom data with FDG uptake
    – Patients with H & N SCC
    – Integrate with ACRIN studies?
- Compare vendor and independent analysis
- Initiate lessons from stage 1

Stage 2b: Correlating Phantom Data with Radiotracer Uptake in Patients

- Multicenter study representing all major manufacturers
- Same phantoms as stage 1
- Compare phantom data with uptake of multiple radiotracers
  - FAZA/F-MISO in patients with H & N SCC, GBM
  - FLT
  - FES in patients with breast cancer
  - F-18 in patients with bone metastases
- Compare vendor and independent analysis
- Build on data analysis form stages 1 and 2a

Stage 2 Outcomes

- Validate stage 1 data

- Correlation of phantom and biological data

- Variables between radiotracers

- Can biological in vivo data be rigorously quantified

- SUV -v- non-SUV based quantification

- Sources of error

- Recommendations for correcting variables

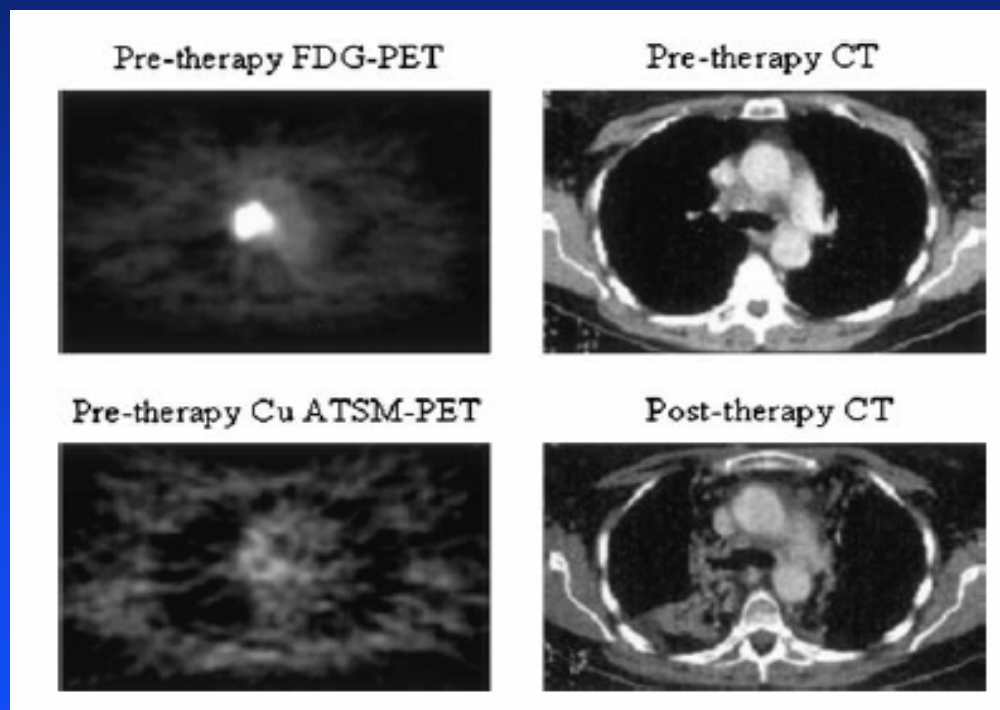**Stage 3:   Quantifying a Specific Imaging Biomarker and Correlating with Outcome:**

Hypoxia imaging for treatment stratification

Progression-free Survival and Overall Survival Based on ^{60}Cu-ATSM Uptake Using Kaplan-Meier Method
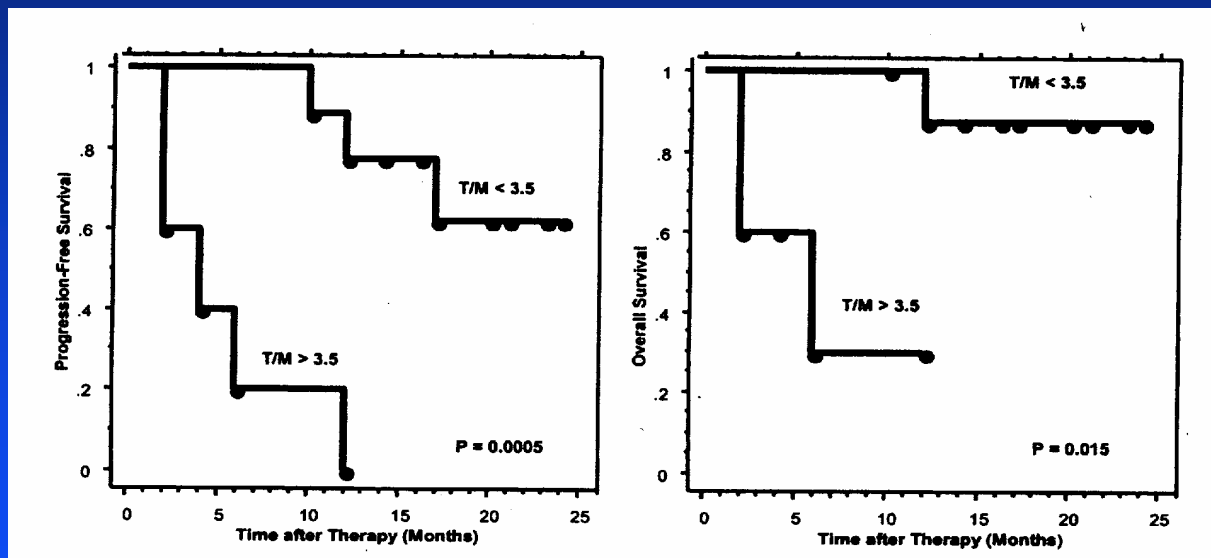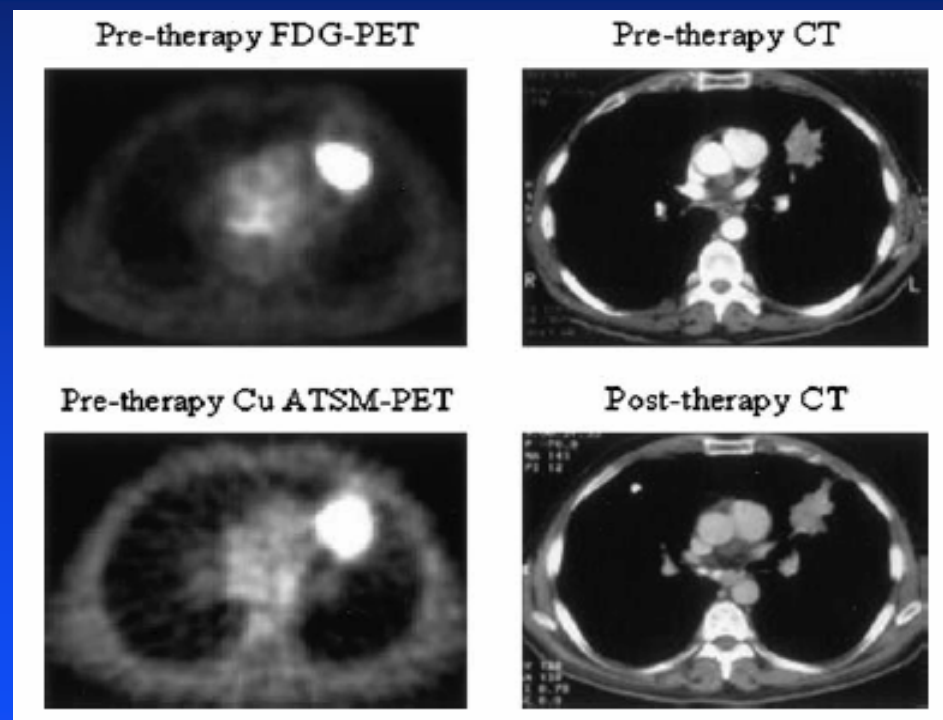

Dehdashti F, et al. *Int J Radiation Oncol Biol Phys* 2003; 55(5):1233-1238

Responder

Dehdashti F, et al. *Eur J Nucl Med Mol Imaging* 2003; 30:844-850
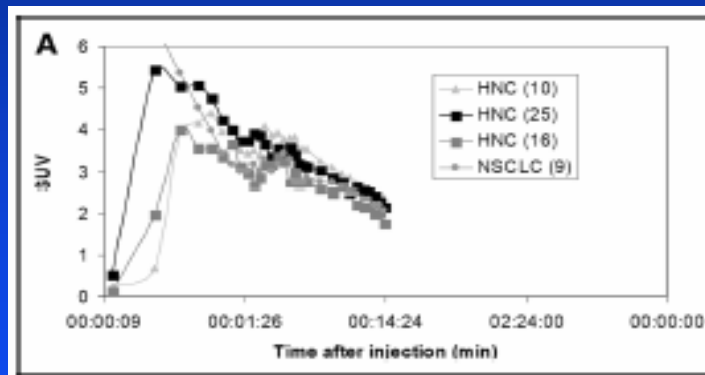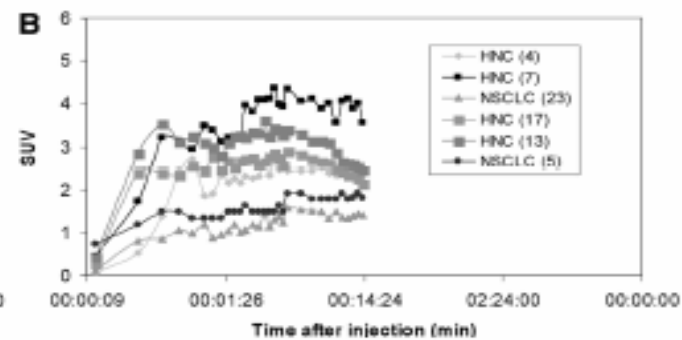
Nonresponder

Dehdashti F, et al. *Eur J Nucl Med Mol Imaging* 2003; 30:844-850

Outcome for Patients with Characteristic Curve Types

Type 1 (washout;
no disease recurrence)

Type 3 (accumulation;
recurrence in 5/6 patients)

Eschmann S-M, *J Nucl Med* 2005; 46:253-260

Stage 3 Strategy

- Link with Phase III pharmaceutical trial
- TPZ - radiosensitizer/hypoxic cell cytotoxic
- Randomized 2 arm study
  - TPZ + Cisplatin/RT
  - Cisplatin/RT
- Comparable methodologies to stage 1 and stage 2
- Can we predict treatment response and stratify for appropriate intervention

TRACE Study Imaging Analysis
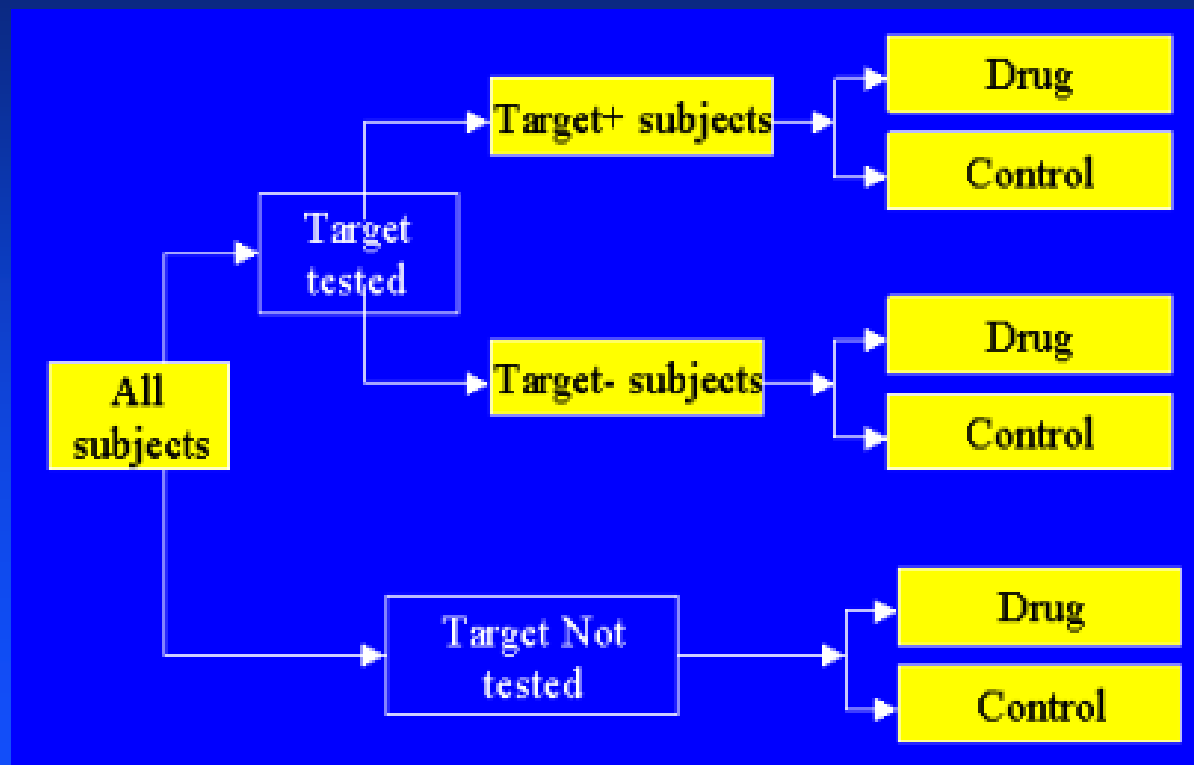
Sub Study Hypothesis

- That the presence of hypoxia demonstrated by imaging will:
  - Predict failure in the control arm
  - Be associated with a good outcome in the treatment arm

"What we're going to do is embark on a long process of cultural change--a change that may not happen, but if it doesn't, medicine will be the poorer."

Brian C. Lentle, M.D.

Molecular Imaging Summit, April, 2005, Oak Brook, Ill.

RSNA News - July, 2005